



Europäisches Patentamt

European Patent Office

Office européen des brevets

⑪ Publication number:

0 294 127

A2

⑫

EUROPEAN PATENT APPLICATION

⑬ Application number: 88304894.4

⑮ Int. Cl.4: B65D 39/00

⑭ Date of filing: 27.05.88

⑬ Priority: 29.05.87 JP 131297/87

⑰ Applicant: DAIKYŌ GOMU SEIKO LTD.
No. 38-2, Sumida 3-chome Sumida-ku
Tokyo(JP)

⑭ Date of publication of application:
07.12.88 Bulletin 88/49

⑰ Inventor: Okuda, Tamotsu c/o Daikyo Gomu
Seiko Ltd
38-2 Sumida 3-chome Sumida-ku
Tokyo(JP)
Inventor: Muraki, Tomoyasu
1-4 Aoyamadai 1-chome
Abiko-shi Chiba-ken(JP)

⑭ Designated Contracting States:
DE FR GB IT

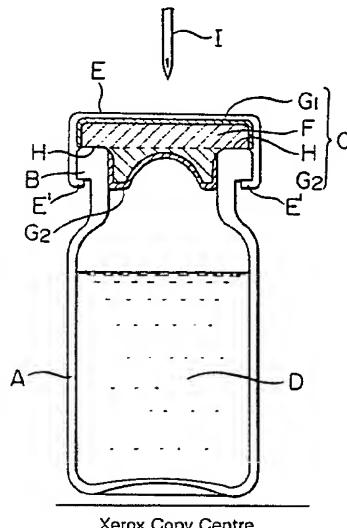
⑰ Representative: Alexander, Thomas Bruce et
al
Boult, Wade & Tenant 27 Furnival Street
London EC4A 1PQ(GB)

⑮ Improvements in resin-laminated rubber stoppers.

⑯ The stopper has a head portion (1) the upper surface of which is laminated with a fluorine resin film (G₁), and a body portion (2) protruding from the head, the body portion being inserted into the vial, and being partly or completely laminated with a fluorine resin film (G₂).

The resin laminated rubber stopper (c) for a medical vial or bottle (A), has better sliding and mechanical transporting properties and reduced contamination due to fine particles from silicone oils and needle piercing fragments.

FIG. I



IMPROVEMENTS IN RESIN-LAMINATED RUBBER STOPPERS

This invention relates to rubber stoppers for bottles or vials and in particular those used for sealing bottles or vials containing vaccines, chemicals, and the like.

The qualities and properties required in Japan of a rubber stopper or closure for medical vials (hereinafter referred to as "rubber stoppers") should be according to the test of a rubber stopper for a liquor transfusion of 11th Revision, Japanese Pharmacopoeia.

Such rubber stoppers are required to satisfy a number of requirements, such as resistance to gas permeability, non-elusive properties, highly clean properties, resistance to chemicals and water absorption, resistance to needle piercing, good self-sealing and sliding properties etc.

In line with these requirements, techniques for laminating rubber stoppers have recently been developed and the inventors and others have proposed rubber stoppers which have good sealing properties, resistance to humidity permeation, good chemical resistance and long storage stability.

These properties are obtained by laminating the part of the surface of the stopper which comes into contact with the contents of the bottle or vial with a fluorine resin film which has good resistance to chemicals. The rest of the surface of the stopper is exposed rubber which gives good air-tightness, as disclosed in Japanese Patent Publication No. 53184/1982, Japanese Patent Laid-Open Publication No. 251041/1985 (US Patent No. 4614276), Japanese Patent Laid-Open Publication Nos. 272134/1986 and 176450/1987 and Japanese Utility Model Laid-Open Publication Nos. 31441/1986 and 17545/1987.

In known rubber stoppers the part of the surface which comes into contact with pharmaceutical chemicals and the like is laminated with a fluorine resin film, but the head or cap portion of the rubber stopper is exposed rubber which is coated with a silicone resin which has good sliding characteristics in order to improve or modify the adhesiveness as the intrinsic property of rubber. This coating is essential for improving the mechanical transporting property of rubber stoppers used in the preparation of drugs and, as increased efficiency in the production of pharmaceutical chemicals is now required as a means for reducing the production costs of pharmaceutical chemicals leading to a reduction in the prices of pharmaceuticals, further improvements in the mechanical transporting, sliding and operating properties etc. of the stoppers is desired.

However, even a very small amount of a silicone resin coating on the head or cap portion of a rubber stopper is transported into a machine for the preparation of a drug and removed into the body portion of the stopper (which is inserted into a bottle or vial), thus resulting in a new problem in that the drug is contaminated with fine particle impurities. In consideration of this problem, it therefore seems preferable to decrease the amount of silicone resin used, but in doing so, the efficiency of production is reduced.

When a rubber stopper is pierced by the needle of a syringe, depending on the thickness, shape, finished state, etc. of the needle, fragments of rubber called piercing-fragments break off from the stopper. This also causes contamination problems. Recently, the thickness of a syringe needle has gradually been decreased and the inner diameter increased without changing the outer diameter, so that the flow rate per unit time is increased, whilst ease of penetration of the needle is ensured. However, the decrease in the thickness of the needle results in an increase in the occurrence of needle piercing fragments.

It is an object of the present invention to provide an improved laminated rubber stopper for a medical bottle or vial, capable of satisfying the above requirements, that is, having better sliding properties and mechanical transporting properties as well as reducing the occurrence of fine particles from the rubber stopper and needle piercing fragments.

The invention is characterised in that both surfaces of the rubber stopper are laminated, the upper surface of a head or cap portion of the rubber stopper being laminated with a fluorine resin film and some or all of a body portion adjacent a lower surface of the head or cap portion of the rubber stopper, which is inserted into the vial, is laminated with a fluorine resin film. The whole surface of the stopper beneath the head or cap portion, including the body portion may alternatively be laminated with a fluorine resin film.

A preferred embodiment of the invention will now be discussed by way of reference to the accompanying drawings, in which;

Fig. 1 is a cross-sectional view of a rubber stopper closing the mouth of a vial and fastened thereto by an aluminum cap.

Fig. 2, Fig. 3 and Fig. 4 are respectively a plan view, a side sectional view taken on line a-a' of Figure 2 and an underneath plan view of one embodiment of the rubber stopper of Fig. suitable for use in a freeze drying method.

Fig. 5 and Fig. 6 are respectively a plan view and a side sectional view taken on line b-b' of Fig. 5 of another embodiment of the rubber stopper of Fig. 1 suitable for use in a reduced pressure gas replacement method.

Fig. 7, Fig. 8 and Fig. 9 are respectively a plan view, a side sectional view taken on line c-c' of Fig. 7 and an underneath plan view of a further embodiment of the rubber stopper of Fig. 1 suitable for use in a freeze drying method.

Fig. 10 and Fig. 11 are respectively a plan view and a side cross-sectional view taken on line d-d' of Fig. 10 of the rubber stopper of Fig. 1 in which the upper surface and lower surface including the body portion of the rubber stopper are completely laminated with a fluorine resin film.

A rubber stopper comprises a head or cap portion at an upper end of the rubber stopper which covers the mouth of a vial, in use, and a body portion provided at a lower end of the rubber stopper beneath and adjacent the head portion, the body portion being inserted into the mouth of the vial.

The body portion and optionally the lower part of the head portion are laminated with a fluorine resin film as described in the prior art and additionally, the upper surface of the head portion is also laminated with a fluorine resin film instead of a silicone coating according to the prior art. Thus, the sliding and mechanical transporting properties of the rubber stopper are largely improved and the occurrence of contaminating fine particle foreign matters from the rubber surface are reduced.

Both the upper surface of a head portion of the rubber stopper and a body under the head are laminated with a fluorine resin film which has a high lubricity to obtain a rubber stopper, in which the occurrence of piercing fragments is remarkably reduced.

As far as the upper surface of the head portion of the stopper is laminated with a fluorine resin film, some or all of the body portion can be laminated with a fluorine resin film such that the sealing means, i.e. a lower surface of the head portion which seals against the vial mouth, comprises an exposed rubber surface and optionally the upper end of the body portion may also be exposed rubber. Of course, the body portion and sealing means can be wholly laminated with a fluorine resin film.

Fig. 1 shows one embodiment of a rubber stopper which can be inserted into the mouth of a vial. In a rubber stopper C, an upper portion of the head portion of the stopper is laminated with a fluorine resin film G₁. The body portion, which is inserted into the mouth of a vial A containing a pharmaceutical chemical D is laminated with a fluorine resin film G₂. When the stopper C is in position a sealing lip H of the head portion contacts the lip of the mouth of the vial A. The lip H is not laminated such that a part F of the rubber is exposed. The vial A is closed by the rubber stopper C, which is covered by an aluminum cap E and fastened to the vial by a flap E'. I is an injection needle.

Figs. 2 to Fig. 4 show another embodiment of the rubber stopper which is suitable for use in a freeze drying method for the preparation of a drug. Items C, G₁, G₂ and H have the same meanings as in the case of Fig. 1. The rubber stopper C comprises a head portion 1, a body portion 2 projecting from a lower surface of the head portion 1, a convex portion 3 on the head portion 1, a concave portion 4 also on the head portion 1, wherein the needle of a syringe enters the stopper. The stopper further comprises sealing means H consisting of a flange surface 5 on the lower side of the head portion 1 and another sealing surface 6 at an upper end of the body portion 2 adjacent flange surface 5, both the sealing means having exposed rubber surfaces. The body portion 2 is cut or notched at two positions to form two legs 7 which are used in a vacuum drying process, the deepest part 8 of the cut portion 7 and protrusions 9 and 10 on the body portion 2 being used for maintaining a vial half closed.

Fig. 5 and Fig. 6 show a further embodiment of the rubber stopper suitable for use in a reduced pressure gas replacement method in which body portion 2 is completely laminated with a fluorine resin film G₂ but a part of the rubber surface on the lower side of the head portion is exposed.

Fig. 7 to Fig. 9 show a further embodiment of the rubber stopper suitable for use in a freeze drying method in which only one cut part 7 is provided.

Fig. 10 and Fig. 11 show yet another embodiment of the rubber stopper corresponding to a modification of that shown in Fig. 5 and Fig. 6, in which all of the upper and lower surfaces of the head portion and the entire surface of the body portion are laminated with a fluorine resin film G₁ and G₂.

The rubber stoppers of the types shown in Fig. 2 to Fig. 9 are suitable for use in preparation of drugs by a positive pressure method wherein the inner pressure of a vial is higher than the atmospheric pressure, or a negative pressure method wherein the inner pressure of a vial is lower than the atmospheric pressure, or a gas replacement method. The rubber stoppers of the types as shown in Fig. 10 and Fig. 11 are suitable for use in preparation of drugs by a normal pressure method wherein the inner pressure of a vial is substantially the same as the atmospheric pressure.

In the present invention, examples of the fluorine resin film used for laminating the upper surface of the head portion of the rubber stopper, a part or all of the body portion or the entire whole lower surface under

the head portion of the rubber stopper including the body portion are tetrafluoroethyleneethylene copolymer (ETFE), tetrafluoroethylene-hexafluoropropylene copolymer (FEP), tetrafluoroethylene-perfluoroalkyl vinyl ether copolymer (PFA), chlorotrifluoroethylene-ethylene copolymer (ECTPE), polyvinyl fluoride (PVF), polyvinylidene fluoride (PVDF), polychlorotrifluoroethylene (PCTFE), polytetrafluoroethylene (PTFE) and the like.

- 5 The fluorine resin used in laminating the upper surface of the head portion and that used for the entire lower surface or for the body surface may be the same or different resins.

The thickness of the fluorine resin film used for laminating the upper surface of the head portion or the surface of a part of all of the body portion is preferably between 0.01 and 0.2 mm. If the thickness of the laminate is less than 0.01 mm, the film tends to break during molding or processing so that the warranty of 10 the quality of the product may be insufficient, whilst if its thickness is more than 0.2 mm, the rigidity of the laminate is too great to maintain proper self-sealing and needle piercing properties.

In order to obtain a strong adhesive surface between a fluorine resin film and a rubber surface, it is preferable to subject the surface of the film to a pretreatment in a conventional manner, for example, corona discharge, plasma discharge, glow discharge, arc discharge, sputter etching, etc. Depending upon the 15 variety of the rubber composition and the fluorine resin film such as PVDF or PVF, etc, a strong adhesive surface can be obtained only by subjecting the surface of the film to a cleaning treatment or primer undercoating treatment, for example, using silicone compounds, epoxy resins, chloroprene rubbers, etc. In any method, it is important to adjust the adhesive strength between the film and the rubber surface to between 1 and 30 Kg/cm.

20 The rubber composition used for a base body of the rubber stopper can be substantially prepared by a prior art technique, i.e. by adding a vulcanizing agent, vulcanization accelerator, vulcanization activator, processing aid, filler, reinforcing agent, etc to at least one member selected from the group consisting of isopreneisobutylene copolymer rubber (IIR), chlorinated or brominated IIR (CIIR, BIIR), acrylonitrile-butadiene copolymer rubber (NBR), acrylonitrile-butadiene-isoprene triple copolymer (NBIR), isoprene rubber (IR), 25 butadiene rubber (BR), styrene-butadiene rubber (SBR), ethylene-propylene rubber (EPM), ethylene-propylene-diene rubber (EPDM), chlorosulfonated polystyrene (CSM), ethylene-vinyl acetate copolymer (EVA), styrene-isoprene rubber (SIR), thermoplastic elastomers, natural rubbers and the like, so that both the physical properties of the stopper and heat resistance can be maintained.

Production of a laminated rubber stopper according to the present invention can be carried out by a 30 process similar to that described in our Japanese Patent Publication No. 53184/1982 and our Japanese Patent Laid-Open Publication No. 272134/1986, which process comprises placing and combining a fluorine resin film, the upper surface of which is surface-treated, and a non-vulcanized rubber sheet, in order, on a lower metal mould which has a recess for forming the body portion of the stopper, pressing and heating them between the lower mould and an upper metal mould to vulcanize and form an intermediate product, 35 cutting or trimming the intermediate product in line with the shape of the body portion, charging again the thus resulting intermediate product in a lower metal mould having a recess corresponding to the body portion, then placing thereon a non-vulcanized rubber sheet, the upper surface of which is laminated with a fluorine resin film, and pressing and heating them beneath an upper metal mould having a recess for forming an enlarged head or flange portion to vulcanize and form a finished product. Thus a rubber stopper 40 of the present invention can be manufactured, in which the upper surface of the head and a part or all of the body portion are laminated with a fluorine resin film, but maintaining an exposed rubber surface on the sealing portion of the head, as shown in Fig. 1 to 9. Another modified process comprises combining and charging a fluorine resin film, non-vulcanized compound rubber sheet and a fluorine resin film stacked in order between an upper metal mould having a recess corresponding to the head portion of the rubber 45 stopper and a lower metal mould having a recess corresponding to the body portion, pressing and heating them to effect vulcanization, forming and then trimming along the outer diameter of the rubber stopper, thus obtaining another rubber stopper of the present invention, in which the upper and lower surface of the rubber stopper are wholly laminated with the fluorine resin film, as shown in Fig. 10 and Fig. 11.

The following examples are given in order to illustrate the present invention without limiting the same.

Examples 1 to 4Parts by Weight

5	Rubber Composition IIR (JSR Butyl 365-commercial name - manufactured by Japan Butyl Co.)	100
10	Zinc Oxide	3
15	Stearic Acid	0.5
20	Clay (Burgess Iceberg-commercial name - made by Burgess Pigments Co.)	60
25	Processing Aid (HI-WAX No. 110 P - commercial name - made by Mitsui Sekiyu Kagaku Co.)	1.2
30	Magnesium Oxide (Kyowamagu 150 - commercial name - made by Kyowa Chemical Industry Co.)	5
35	White Carbon (Carplex 1120 - commercial name - made by Shionogi Seiyaku Co.)	10
	Titanium Oxide	3
	Sulphur	0.7
	Zinc Di-n-butyldithiocarbamate	0.7
	Zinc Diethyldithiocarbamate	0.5

The above described rubber composition was kneaded using two rolls according to a method described in "The Society of Rubber Industry Japan Standard" (1979) and then used for the preparation of a rubber stopper as shown in Fig. 6 by a process comprising forming a rubber stopper simultaneously with 40 laminating it with various fluorine resin films. The body portion was laminated with the following ETFE film 1) in every case, while the head portion was laminated with the following four fluorine resin films 1) to 4), these fluorine resin films being manufactured by Daikin Kogyo Co. and subjected to a sputter etching treatment on one side and having a thickness of 75 μm :

- 45 Example 1) ETFE film: Neoflon ETFE -commercial name-
- Example 2) PTFE film: Polyflon TFE -commercial name-
- Example 3) PFA film: Neoflon PFA -commercial name-
- Example 4) FEP film: Neoflon FEP -commercial name-

The above described fluorine resin film of Example 1) for G_2 and a non-vulcanized compound rubber were stacked and placed on a lower metal mould, after which an upper metal mould was placed thereon 50 and the rubber was compressed and heated at a temperature of $150^\circ\text{C} \pm 1^\circ\text{C}$, thereby forming and vulcanizing a rubber stopper simultaneously with laminating the body portion of the rubber stopper. Then, the resulting intermediate product was cut or trimmed to a predetermined size and the cut or trimmed body portion was charged in the lower metal mould, on which were placed, in order, a non-vulcanized compound rubber 1, one of the foregoing resin films 1) to 4) for G_1 and an upper metal mould having a recess for 55 forming the head portion, and pressed with heating at a temperature of $150 \pm 1^\circ\text{C}$, thus obtaining a rubber stopper as shown in Fig. 6, followed by cutting a separate into individual stoppers and washing.

Comparative Example 1:

For comparison, on the other hand, a comparative sample 1 was prepared in an analogous manner to that described above, although the head portion was not laminated (Comparative Example 1), and surface-treating or laminating the head by the prior art methods to obtain rubber stoppers each having a shape as shown in Fig. 6 (Comparative Examples 2 to 4).

Comparative Example 2: silicone A method

10 The rubber surface of the head portion was coated twice with a silicone emulsion diluted 30 times with water, using a brush.

Comparative Example 3: silicone B method

The rubber surface of the head portion was coated twice with an isopropyl alcohol solution containing 1.2% by weight of a silicone oil, using a brush.

Comparative Example 4:

The rubber surface of the head portion was coated with a polypropylene film (Mitsui Polypro -commercial name- manufactured by Mitsui Sekiyu Kagaku Co., 75 μm thickness).

25 The resulting products (Examples 1 to 4) and the comparison products (Comparative Examples 1 to 4) were subjected to the following tests, obtaining results as shown in the following table:

I LEGAL TESTS

30

i) Elution Test

35 - The properties of the samples were tested according to "Test Method of Rubber Stopper for Liquid Transfusion" of 11th Revision, Japanese Pharmacopoeia by the foaming test, pH, zinc, potassium permanganate reducing materials, distillation residues and ultraviolet absorption spectra.

ii) Fragmentation Test

40 - Fragments occurring when a needle penetrated the rubber stopper sample were counted to obtain the number of the fallen fragments (rubber fragments/100 times needling) according to British Standard 3263 (1960), Fragmentation Test.

45

II PROPERTY TESTS

50

i) Measurement of the Friction Coefficient of the Head portion of Rubber Stopper (Inclination Method)

A polished flat surface of a stainless plate was wiped with a solvent and adequately dried, and the rubber stopper sample was placed thereon in such a manner that the head portion of the rubber stopper was directed downwards. The stainless steel plate was inclined at an angular velocity of 0.3°/ sec and the angle at which the rubber stopper started to slide was measured. From the measured angle θ , the coefficient of friction μ was calculated by the following formula:

Coefficient of Friction (μ) = $\tan \theta$ (Coulomb Friction)

ii) Measurement of Quantity of Silicone Adhered (μg)

- 5 - 100 ml of chloroform was added to 10 samples of the stoppers and shaken to extract Si, the quantity of which was measured by the atomic absorptiometric analysis and calculated as a quantity of dimethylpolysiloxane (μg) from the calibration curve.

iii) Fine Particle Test

- 10 - 100 ml of dust-free water (at most 10 fine particles of at least 2 μm per 10 ml) was added to 10 samples of the rubber stoppers, shaken moderately for 20 minutes and allowed to stand for 30 minutes to obtain test liquors. The number of fine particles of at least 2 μm in 10 ml of the test liquor was counted by means of an automatic fine particle counter (Royco Automatic Particle Counter -commercial name-).

15

iv) Water Absorption Test

- 20 - 5 samples of the rubber stopper were placed in a 100 ml beaker, dried at a temperature of 65 ± 1 °C for 24 hours, allowed to cool for 15 minutes in a P_2O_5 dessicator and then precisely weighed to give weight A. These samples were then subjected to disinfection in a water autoclave at a temperature of 121 ± 1 °C for 30 minutes, allowed to cool in the P_2O_5 desicator for 15 minutes and then precisely weighed again to give weight B. The water absorption ratio is calculated by the following formula:

25

Water Absorption Ratio (%) =

$$\frac{B - A}{A}$$

30

 $\times 100$ v) Heat Resistance Test (Deterioration Confirmation Test)

- 35 - 5 samples of the rubber stopper disinfected in the autoclave at 121 °C for 1 hour were dried at 150 °C for 3 hours and the change in the surface was observed while magnifying 10 times by a loupe. The head part of the rubber stopper was strongly pushed against an aluminum foil and the

40

45

50

55

5
10
15
20
25
30
35
40
45
50
55

Table 1

Test Items	I	Example 1	Example 2	Example 3	Example 4	Comparative		Comparative		Comparative	
						Example 1	Example 2	Example 3	Example 4	Comparative Example 1	Comparative Example 2
Property											
430 nm (A)	ETFE	100.0	100.0	100.0	100.0	99.5	99.0	99.3	99.5	99.0 or more	
650 nm (A)	ETFE	100.0	100.0	100.0	100.0	99.3	98.0	99.0	99.5	99.0 or more	
Foaming(min)	0.1	0.1	0.1	0.1	0.3	2.8	0.6	0.6	0.2	disappear in 3 min	
pH	0.23	0.21	0.30	0.29	0.68	0.74	0.63	0.63	0.55	1.0 or less	
Zinc (μg/ml)	<0.01	<0.01	<0.01	<0.01	0.3	0.5	0.5	0.5	0.2	1 or less	
KMnO ₄ Reducing Material (ml)	0.09	0.12	0.10	0.12	0.92	1.82	1.37	1.37	0.53	2.0 or less	
Distillation Residue (mg)	<0.01	<0.01	<0.01	<0.01	2.1	3.6	2.3	2.3	0.4	2.0 or less	
UV Absorption Spectrum	0.003	0.002	0.003	0.002	0.17	0.23	0.19	0.19	0.12	0.20 or less	
Eruption Test (Japanese Pharmacopoeia)											

Table 1 (continued)

Property Test	B S	Number of Fragments (rubber frag- ments/100 times)	0	0	0	1	47	16	12	73	20 or less
Friction Coefficient of Head Part	0.51	0.16	0.40	0.40	>1(III)	1.0	0.93	0.23			
Amount of Silicone Adhered (ug)	0	0	0	0	0	615	248	0			
Fine Particles (number/10ml)	16	25	21	30	985	35.581	8.160	395			
Water Absorption(t)	<0.01	<0.01	<0.01	<0.01	1.2	0.4	0.3	0.1			
Heat Resistance	no change	no change	no change	no change	more adhesive	somewhat adhesive	somewhat yellow adhesive				
Synthetic Estimation	○	○	○	○	○	○	○	△	△	△	△

Note: I = Lamination of Head portion of Rubber Stopper

II = Laminating Material or Treating Method of Head portion of Rubber Stopper

III = Impossible to Measure

degree of the adhesion thereof was judged. The test results of Table 1 can be estimated as follows:

Elution Test

5

All the samples satisfy the standard of the Japanese Pharmacopoeia except Comparative Example 1 which had no laminating film on its head portion, which gave a distillation residue of 3.6 mg. In particular, the samples of the present invention, Examples 1 to 4 all gave satisfactory results.

10

Number of Fragments

The Examples 1 to 4 showed fewer fragments, Comparative Examples 2 and 3 both treated with silicone are next to these samples and in the case of Comparative Example 1 having no laminating film and 15 Comparative Example 4 having a laminated PP film, there occurred a number of fragments.

Friction Coefficient

20 In the case of Examples 1 to 4 in which the head portions of the stoppers were laminated with fluorine resins, ETFE, PTFE, PFA and FEP according to the present invention and Comparative Example 4 in which the head portion was laminated with PP, the friction coefficient against the stainless steel plate is lowered to a greater extent, thus resulting in far better sliding and mechanical transporting properties than in the case of Comparative Example 1 in which the rubber surface of the head portion was exposed and Comparative 25 Examples 2 and 3 in which the head portion was treated with the silicone oil.

Quantity of Silicone Adhered to Surface of Rubber Stopper

30 In the case of Examples 1 to 4 in which the head portions were laminated with fluorine resin films and Comparative Example 4 in which the head portion was laminated with PP, no silicone was found adhered to the surface whilst in the case of Comparative Examples 2 and 3 in which the head portions were respectively treated with the silicone emulsion and silicone oil, large amounts of silicone were detected.

35

Fine Particle Test

In Examples 1 to 4 according to the present invention, much fewer fine particles were found, whilst in Comparative Examples 2 and 3, a large number of fine particles were found. In the case of Comparative 40 Example 4 in which the head portion was laminated with PP, a number of fine particles were also found.

Water Absorption Test

45 The water absorption ratio of the rubber stoppers in Examples 1 to 4 according to the present invention was very low, i.e. 1/10 to 1/120 times less than that of Comparative Examples 1 to 4.

Heat Resistance Test

50

Observation of the upper surface of the head portion showed that in Examples 1 to 4, there was no change, whilst in Comparative Examples 1 to 3, adhesiveness occurred and in Comparative Example 4, a colour change on the surface of the PP film occurred, thus showing occurrence of thermal deterioration.

55

Synthetic Estimation

It will clearly be understood from these test results that the samples of the stoppers made according to the present invention as shown in Examples 1 to 4 are suitable (mark ②) as rubber stoppers or closures for use in the preparation of drugs or pharmaceutical chemicals, whereas the samples of Comparative Examples 1 and 2 could not be used (mark x). Those of Comparative Examples 3 and 4 can be used, but meet with some problems of lack of heat resistance, and the occurrence of a number of fine particles and fragments (mark Δ).

The difference in advantages or effects between the samples of the present invention and the comparison samples and of the prior art is clear from the foregoing illustrations and results of Examples 1 to 4 and Comparative Examples 1 to 4. That is, the laminated rubber stopper according to the present invention has the following advantages:

- (1) The rubber stopper of the present invention shows very little eluate or elution materials.
 - (2) Occurrence of fine particles due to silicones can be prevented because no silicone coating is necessary.
 - (3) The rubber stopper of the present invention shows little water absorption during washing or disinfecting, thus increasing the efficiency of treating the rubber stopper, for example, shortening the required treating time.
 - (4) The rubber stopper of the present invention has better mechanical properties at high speed.
 - (5) The surface lubricity is increased and occurrence of fragments during needle penetration can be prevented.
 - (6) Mechanical contamination due to the transfer of a silicone can be prevented.
 - (7) The rubber stopper of the present invention, having little adhesiveness, can stably be mass-produced as it will not adhere to the upper plate of a freeze-drying machine.
- Therefore, the drug or pharmaceutical production speed can effectively be increased by the use of the rubber stopper of the present invention, from which a large decrease of the drug production cost can be expected. On the other hand, since occurrence of fine particles can be remarkably reduced in the rubber stopper of the present invention, although a number of fine particles occur due to a silicone in the rubber stopper of the prior art, it is possible to achieve a pharmaceutical preparation with high quality. Moreover, occurrence of fragments due to needle penetration can be prevented.
- As described above, the laminated rubber stopper of the present invention is capable of exhibiting better properties at any stage of preparation of a drug using a medical vial, storage and application and thus largely serve to a medical vial preparation with a high quality.

35

Claims.

1. A resin laminated rubber stopper (c) for a medical vial or bottle (A), having a rubber body (2) for insertion into the mouth (B) of the vial or bottle, and a head (1) having an upper and a lower surface (5), the body protruding from the lower surface of the head, characterised in that the upper surface of the head is laminated with a fluorine resin film (G₁) and at least a part of a surface of the body is laminated with a fluorine resin film (G₂).
2. A resin laminated rubber stopper (c) as claimed in claim 1 characterised in that the entire surface of the body (2) is laminated with a fluorine resin film (G₂).
3. A resin laminated rubber stopper (c) as claimed in claim 1 or claim 2, characterised in that the lower surface of the head (5) is laminated with a fluorine resin (G₂).
4. A resin laminated rubber stopper (c) as claimed in claim 1, claim 2 or claim 3, characterised in that the fluorine resin film (G₁, G₂) is of a member selected from the group consisting of tetrafluoroethylene-ethylene copolymers, tetrafluoroethylene-hexafluoropropylene copolymers, tetrafluoroethylene-perfluoroalkyl vinyl ethers copolymers, chlorotrifluoroethylene-ethylene copolymers, polyvinyl fluoride, polyvinylidene fluoride, polychlorotrifluoroethylene and polytetrafluoroethylene.
5. A resin laminated rubber stopper (c) as claimed in any one of the preceding claims, characterised in that the thickness of the fluorine resin film (G₁, G₂) is in the range of 0.01 to 0.2 mm.
6. A resin laminated rubber stopper (c) as claimed in any one of the preceding claims, characterised in that the fluorine resin film (G₁, G₂) is subjected to pretreatment by corona discharge, plasma discharge, glow discharge, arc discharge or sputter etching.
7. A resin laminated rubber stopper (c) as claimed in any one of the preceding claims, characterised in that the fluorine resin film (G₁, G₂) is cleaned or undercoated with a primer.

8. A resin laminated rubber stopper (c) as claimed in claim 7, characterised in that the primer is selected from the group consisting of silicone compounds, epoxy resins and chloroprene rubbers.

5

10

15

20

25

30

35

40

45

50

55

FIG. 1

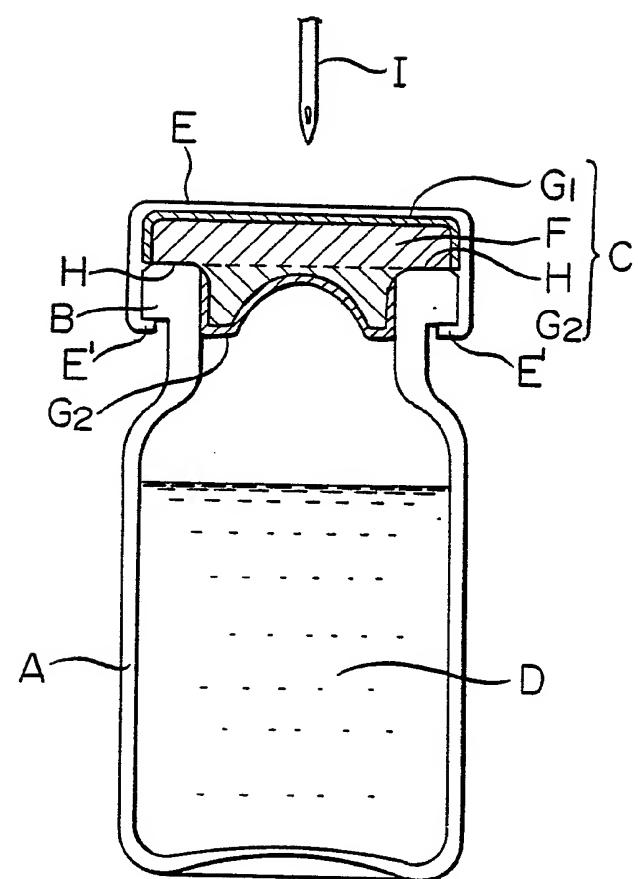


FIG. 2

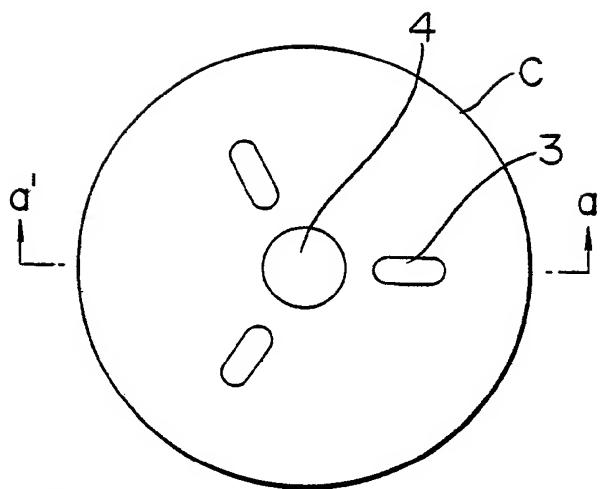


FIG. 3

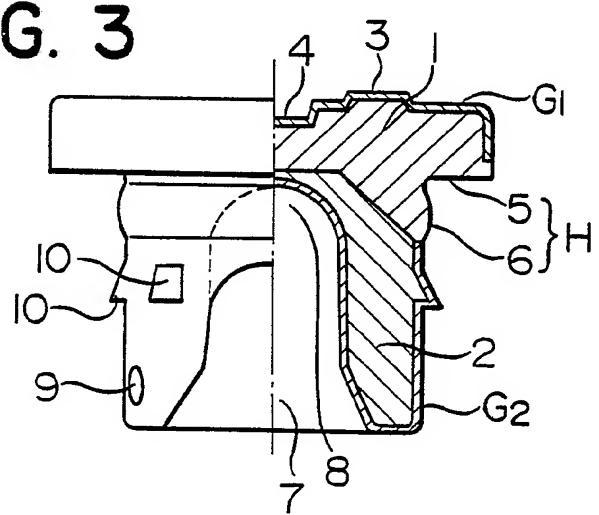


FIG. 4

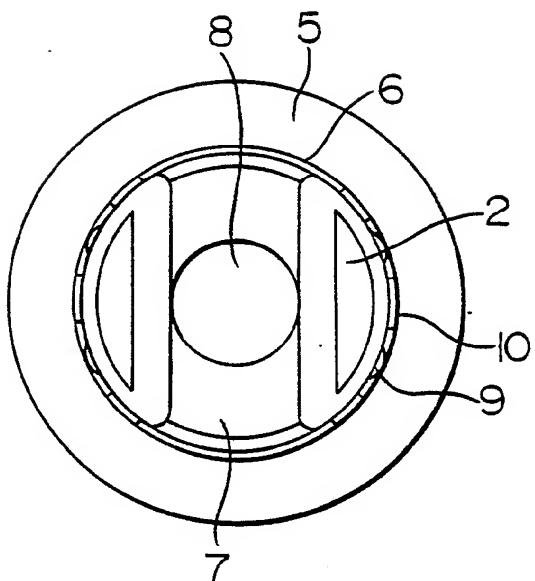


FIG. 5

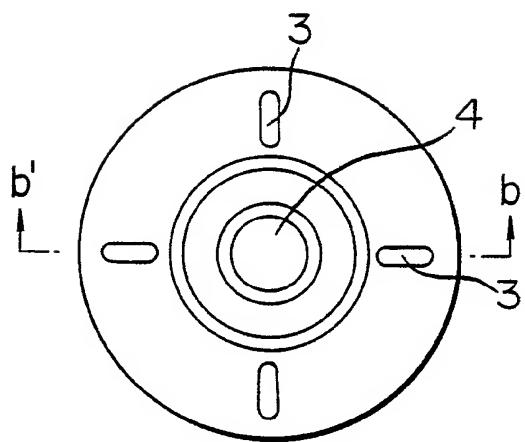


FIG. 6

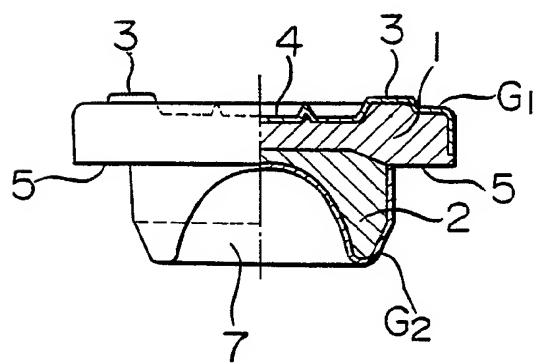


FIG. 7

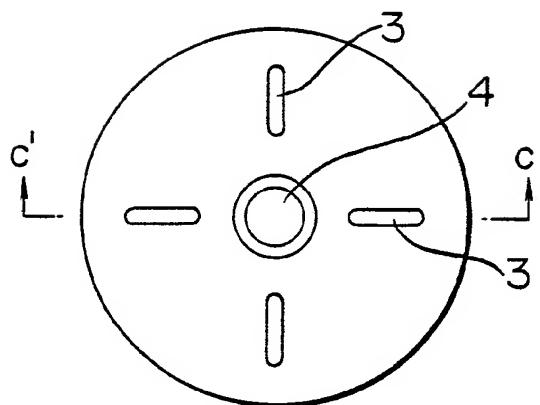


FIG. 9

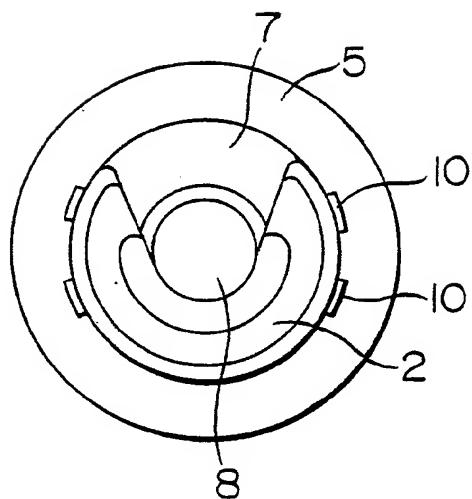


FIG. 8

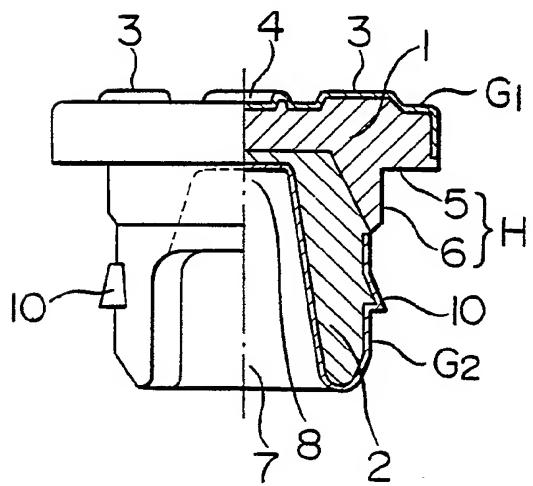


FIG. 10

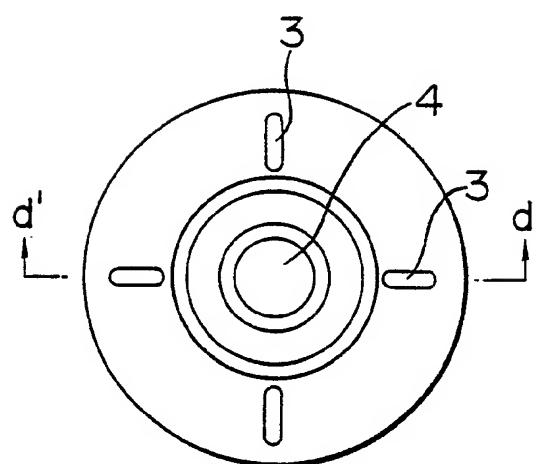


FIG. 11

